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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,978	11/24/2003	Gregg Budahazi	1530.0550001/JUK/JCI	1745

26111 7590 05/19/2008

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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
05/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,978	BUDAHAZI ET AL.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *1-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 9, 2008 has been entered.

2. Claims 1-39 were previously pending with claims 1-20 withdrawn from consideration. Applicants amended claims 21 and 22 and added new claim 40. Claims 21-40 will be examined.

3. Applicants' amendments overcame the rejection of claims 21 and 24-29 under 35 U.S.C. 102(b) as anticipated by Nochumson et al. and the rejection of claims 22 and 23 under 35 U.S.C. 103(a) over Nochumson et al. All other previously presented rejections are maintained for reasons given in the "Response to Arguments" section below.

Response to Arguments

4. Applicant's arguments filed April 9, 2008 have been fully considered but they are not persuasive.

A) Regarding the interpretation of the term "about" Applicants argue that:

"A person of ordinary skill in the art of DNA production would understand that the use of the term "about" with the recited numerical ranges merely allows for the small margin of error that may be associated with the instruments used to determine the purity of the claimed product."

First, Applicants did not define the term. Second, Applicants did not present the results of measurements of RNA concentration or protein concentration in the samples examined; therefore one of ordinary skill in the art cannot determine what is the detection limit and error associated with

such measurements. For the endotoxin level measurements, Applicants show that a standard deviation of the measurement in four samples (page 32, [0117]) was 100% of the measurement value, i.e. the result was 0.0001 EU/μg ± 0.0001 EU/μg of product, and for the host cell DNA levels it was 60%, i.e. 0.0005 μg /μg ± 0.0003 μg /μg of product. Therefore, these measurement results indicate not a "small margin of error" but a margin of between 60 and 100% of the measured value. As the amounts of RNA and protein claimed are extremely small as well, it is reasonable to assume that the measurement error would be of the same order.

B) Regarding the rejection of claims 30-39 under 35 U.S.C. 112, second paragraph, Applicants argue that the claims are not indefinite, since "any impurities in the claimed DNA products are so minute that LAL assay, Southern blot assay, chromatography, Northern blot assay and ethidium bromide analysis are simply not sensitive enough to detect them under any conditions" (page 8 of the response).

However, claims 30-39 are not dependent from claim 21 or any other claim listing specific concentrations of impurities. Therefore, a limitation "undetectable by Southern blot assay", for example, does not provide guidance of what the concentration of the impurity is, considering that the amount of DNA detectable by Southern blot depends on the hybridization conditions such as temperature and salt concentration as well as on the total amount of DNA tested and the amount of background DNA present in the sample. Thus, such limitation does not provide metes and bounds for the level of DNA impurties in the plasmid preparation. The same argument holds true for all of the other detection methods listed in these claims.

The rejection is maintained.

C) Regarding the rejection of claims 30-39 under 35 U.S.C. 102(b) as anticipated by Nochumson et al., Applicants argue that the RNA in DNA product of Nochumson et al. is several orders of magnitude less than claimed in claims 21-39.

However, independent claim 30 does not depend from any of the claims 21-29, therefore does not contain any numerical limitations concerning the RNA or other impurities concentration.

The rejection is maintained.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 30-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 30-39 are indefinite in claim 30. Claim 30 is indefinite over the recitation of "wherein said DNA product contains an amount of host cell derived impurities that is undetectable by any one of a group consisting of: LAL assay, Southern blot assay, chromatography, Northern blot assay, and ethidium bromide agarose analysis."

It is not clear what are the meets and bounds of this claim. As the detection limit of any particular assay depends on the conditions under which it is performed as well as the ingredients used, the level of impurities detected will depend on where and how the assay is performed. Applicants did not specify conditions and cutoff values for any of these assays which would result in undetectable levels of impurities.

Claim Interpretation

7. Applicants did not define the term "about X units", therefore any reasonable value below or above a given number X is considered to anticipate this term. For the endotoxin level measurements, Applicants show that a standard deviation of the measurement in four samples (page 32, [0117]) was 100% of the measurement value, i.e. the result was 0.0001 EU/μg ± 0.0001 EU/μg of product, and for the host cell DNA levels it was 60%, i.e. 0.0005 μg /μg ± 0.0003 μg /μg of product. Therefore, these measurement results indicate not a "small margin of error" but a margin of between 60 and 100% of the measured value. As the amounts of RNA and protein claimed are extremely small as well, it is reasonable to assume that the measurement error would be of the same order, and, therefore, taking into account guidance from the specification, the term "about" is considered to indicate values between 60 and 100% of the given numerical value.

8. In view of the indefiniteness of claims 30-39, any level of impurities is considered as anticipatory of these claims.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 30-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Nochumson et al. (US 2001/0034435 A1; cited in the IDS and in the previous office action).

Regarding claims 30-39, Nochumson et al. teach plasmid DNA and pharmaceutical preparation (page 8, [0099]). Nochumson et al. teach plasmid DNA preparation with 95% plasmid DNA and less than 5% RNA, anticipating the limitation of undetectable amount of RNA product (page 8, [0099]). Nochumson et al. teach plasmid DNA preparation with 0.05% of host DNA (page

8, [0099]), which is equivalent to 0.0005 μg of host DNA/μg of DNA product, therefore Nochumson et al. anticipate the limitation of undetectable amount of the host genomic DNA. Nochumson et al. teach plasmid DNA preparation with less than 0.06% of protein (page 8, [0099]), which is equivalent to 0.0006 μg of protein/μg of DNA product, therefore Nochumson et al. anticipate the limitation of undetectable amount of protein. Nochumson et al. teach plasmid DNA preparation with less than 0.2EU/mg of endotoxin, which equals less than 0.0002 EU/μg (page 8, [0099]), anticipating the limitation of undetectable amount of endotoxins (=pyrogens). They teach pharmaceutical preparations (claims 8, 11, 19, 31).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 21-29 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nochumson et al. (US 2001/0034435 A1; cited in the IDS and in the previous office action),

Kvederas et al. (US 2003/0109696 A1) and Cooke et al. (J. Biotechnol., vol. 85, pp. 297-304, February 2001).

A) Regarding claims 21-29 and 40, Nochumson et al. teach plasmid DNA and pharmaceutical preparation (page 8, [0099]). Nochumson et al. teach plasmid DNA preparation with 95% plasmid DNA and less than 5% RNA (page 8, [0099]). Nochumson et al. teach plasmid DNA preparation with 0.05% of host DNA (page 8, [0099]), which is equivalent to 0.0005 μg of host DNA/μg of DNA product, therefore Nochumson et al. anticipate the range from about 0.00002 to about 0.002 μg of host DNA/μg of DNA product and the range of from about 0.00004 to about 0.0004 μg of host DNA/μg of DNA product. Nochumson et al. teach plasmid DNA preparation with less than 0.06% of protein (page 8, [0099]), which is equivalent to 0.0006 μg of protein/μg of DNA product, therefore Nochumson et al. anticipate the range from about 0.00000001 to about 0.001 μg of protein/μg of DNA product. Nochumson et al. teach plasmid DNA preparation with less than 0.2EU/mg of endotoxin, which equals less than 0.0002 EU/μg of DNA product (page 8, [0099]), anticipating the range of less than 0.01 EU/μg and the range from about 0.00001 EU to 0.0001 EU/μg of DNA product as well as the range from about 0.0001 EU to 0.0002 EU/μg of DNA product. They teach pharmaceutical preparations (claims 8, 11, 19, 31).

Regarding claims 24 and 27, Nochumson et al. teach plasmid DNA preparation with 0.05% of host DNA (page 8, [0099]), which is equivalent to 0.0005 μg of host DNA/μg of DNA product, therefore Nochumson et al. anticipate the limitations of about 0.00004 and of about 0.0005 μg of host DNA/μg of DNA product.

Regarding claims 25 and 26, Nochumson et al. teach plasmid DNA preparation with less than 0.2EU/mg of endotoxin, which equals less than 0.0002 EU/μg (page 8, [0099]), anticipating the values of about 0.0002 and about 0.0001 EU/μg of DNA product.

B) Nochumson et al. do not teach RNA contaminant levels from about 0.00001% to about 0.0001%.

C) Kvederas et al. teach a method of plasmid DNA purification from bacterial cells which results in a 100% removal of bacterial RNA from the preparation, i.e. the final concentration of RNA is 0% (Abstract; page 14, 15, Tables 3 and 4).

Cooke et al. teach removal of RNA from plasmid preparations using host cells expressing a ribonuclease (Abstract; page 299, second paragraph).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have further purified the plasmid of Nochumson et al. to achieve the total removal of RNA in the plasmid preparation as taught by Kvederas et al. The motivation to do so, provided by Kvederas et al., would have been, as stated on page 1, [0005]:

"One feature, however, is that certain substances present in the bacterial biomass, among them polysaccharides derived from the bacterial cell wall, lipopolysaccharides and RNA, are difficult to remove without several chromatographic steps, and tend to contaminate the standard DNA preparations. Some of these bacterially derived contaminants are extremely potent effectors of various defence systems of higher eukaryotes, possibly because of their intrinsic function as a signal of bacterial infection. The elimination of these contaminants is a major problem in the manufacture and purification of plasmid DNA."

Further, one of ordinary skill in the art would realize that introduction of bacterial RNA, even in small amounts, might result in some level of expression of bacterial proteins within

transfected cells, causing unforeseen and potentially lethal complications. As stated by Cooke et al. (page 298, second paragraph):

"The introduction to patients of plasmid or host nucleic acid sequences that are potentially oncogenic, immunogenic, or that encode antibiotic resistance genes, is of particular concern (Williams et al., 1998). As such, host RNA contamination of a recombinant therapeutic product must be minimised, particularly for therapies that require multiple patient dosing (DiPaolo et al., 1999)."

14. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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May 15, 2008